

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **20-718**

CHEMISTRY REVIEW(S)

FEB 19 1998

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG
PRODUCTS**

Review of Chemistry, Manufacturing, and Controls

NDA 20-718 CHEM. REVIEW #: 3 REVIEW DATE: January 20, 1998

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Amendment	1/6/1998	1/7/1998	1/8/1998

NAME & ADDRESS OF APPLICANT:

COR THERAPEUTICS, INC.
256 E. Grand Avenue
South San Francisco, CA 94080

DRUG PRODUCT NAME

<u>Proprietary:</u>	Integrilin™ Injection
<u>Nonproprietary/USAN:</u>	Eptifibatide
<u>Code Name/#:</u>	30.002
<u>Chem. Type/Ther. Class:</u>	1S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL. CATEGORY/INDICATION: Antithrombotic agent.

As an adjunct to aspirin and heparin in patients undergoing percutaneous transluminal coronary angioplasty for the prevention of acute cardiac ischemic complications (death, myocardial infarction, need for urgent intervention) related to abrupt closure of the treated coronary vessel.

DOSAGE FORM:

Solution

STRENGTHS:

Bolus vial (2 mg/ml, 10 ml)
Infusion vial (0.75 mg/ml, 100 ml)

ROUTE OF ADMINISTRATION:

Intravenous

DISPENSED:

☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

Cyclo(S-S)-mercaptopropyl-(L)homoarginyl-glycyl-(L)aspartyl-(L)tryptophanyl-(L)propyl-(L)cysteinamide

Molecular Formula: C₃₅H₄₉N₁₁O₉S₂

Molecular Weight: 832

CONCLUSIONS & RECOMMENDATIONS:

The amendment contains satisfactory information regarding Chemistry, Manufacturing, Control for the drug product. However, I still have two concerns regarding this application:

The first concern deals with the amount of impurities/degradation present in the drug product. I have some reservation regarding the specification limit for the impurities/degradation generated in the drug product (stored at room temperature) I think this limit is too high regardless of the safety nature/potency of these impurities.

The second concern is that this amendment contains many Toxicological/Clinical issues that it has to be reviewed, not only by the chemistry reviewer, but also by other members of the reviewing team—(Pharmacologist/Medical Officer).

2/19/98

Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

2/19/98

Eric Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:

Orig. NDA 20-718
HFD-180/Division file
HFD-180/LTalarico
DISTRICT OFFICE
HFD-180/CSO/JDuBeau
HFD-110/CSO/ZMcDonald
HFD-180/AAl-Hakim
R/D Init: EDuffy/2-19-1998
AAA/dob F/T 2-19-98/WP: c:\wpfiles\chem\N\20718801.3aa

FEB 19 1998

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG
PRODUCTS**

Review of Chemistry, Manufacturing, and Controls

NDA 20-718**CHEM. REVIEW #: 2****REVIEW DATE:** January 06, 1998

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	4/01/1996	4/02/1996	4/10/1996
Amendment	6/14/1996	6/17/1996	7/17/1996
Amendment	6/26/1996	6/28/1996	7/17/1996
Amendment*	7/23/1997	7/25/1997	8/13/1997
Amendment*	9/30/1997	10/1/1997	10/3/1997

* This review deals with the above two amendments

NAME & ADDRESS OF APPLICANT:COR THERAPEUTICS, INC.
256 E. Grand Avenue
South San Francisco, CA 94080**DRUG PRODUCT NAME**

<u>Proprietary:</u>	Integrilin™ Injection
<u>Nonproprietary/USAN:</u>	Eptifibatide
<u>Code Name/#:</u>	30.002
<u>Chem. Type/Ther. Class:</u>	1S

ANDA Suitability Petition/DESI/Patent Status: N/A**PHARMACOL. CATEGORY/INDICATION:** Antithrombotic agent.

As an adjunct to aspirin and heparin in patients undergoing percutaneous transluminal coronary angioplasty for the prevention of acute cardiac ischemic complications (death, myocardial infarction, need for urgent intervention) related to abrupt closure of the treated coronary vessel.

DOSAGE FORM:

Solution

STRENGTHS:Bolus vial (2 mg/ml, 10 ml)
Infusion vial (0.75 mg/ml, 100 ml)**ROUTE OF ADMINISTRATION:**

Intravenous

DISPENSED:☒ Rx ☐ OTC**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:**

Cyclo(S-S)-mercaptopropyl-(L)homoarginyl-glycyl-(L)aspartyl-(L)tryptophanyl-(L)propyl-(L)cysteinamide

Molecular Formula: C₃₅H₄₉N₁₁O₉S₂**Molecular Weight:** 832

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable):

See Chemistry Review No. 1 dated July 25, 1996.

CONSULTS:

Statistics
Environmental Assessment
Microbiology

REMARKS/COMMENTS:

This is a review of the major chemistry amendment submitted by COR Therapeutics. The amendment also contains responses to our information request letter (included in the action letter) dated 3/21/1997.

CONCLUSIONS & RECOMMENDATIONS:

The amendment provided satisfactory responses to our information request letter. However, the impurities/degradants specification limit for the new stability protocol is too high. This issue will be communicated to the firm (see comment on page 34 of this review).

2/19/98

Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

2/19/98

Eric Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:

Orig. NDA 20-718

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HFD-180/AAl-Hakim

R/D Init: EDuffy/2-19-1998

AAA/dob F/T 2-19-98/WP: c:\wpfiles\chem\N\20718801.2aa

Duffy

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG
PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA 20-718 CHEM.REVIEW #: 1 REVIEW DATE: July 25, 1996

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	4/01/1996	4/02/1996	4/10/1996
Amendment	6/14/1996	6/17/1996	7/17/1996
Amendment	6/26/1996	6/28/1996	7/17/1996

NAME & ADDRESS OF APPLICANT:

COR THERAPEUTICS, INC.
256 E. Grand Avenue
South San Francisco, CA 94080

MAR 10 1997

DRUG PRODUCT NAME

<u>Proprietary:</u>	Integrilin
<u>Nonproprietary/USAN:</u>	Intrifiban Injection (pending)
<u>Code Name/#:</u>	30.002
<u>Chem.Type/Ther.Class:</u>	1S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: Antithrombotic agent.

As an adjunct to aspirin and heparin in patients undergoing percutaneous transluminal coronary angioplasty for the prevention of acute cardiac ischemic complications (death, myocardial infarction, need for urgent intervention) related to abrupt of the treated coronary vessel.

DOSAGE FORM: Solution

STRENGTHS: Bolus vial (2 mg/ml, 10 ml)
Infusion vial (0.75 mg/ml, 100 ml)

ROUTE OF ADMINISTRATION: Intravenous

DISPENSED: ✓ Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Cyclo(S-S)-mercaptopropyl- (L) homoarginyl-glycyl- (L) aspartyl-
(L) tryptophanyl- (L) propyl- (L) cysteinamide

Molecular Formula: C₃₅H₄₉N₁₁O₉S₂

Molecular Weight: 832

Structural Formula: see next page

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable pending adequate responses to queries regarding some items in the drug substance and the drug product. The major queries are related to:

- Holding time for the drug substance by Cor Therapeutics.
- Holding time for the drug product before distribution.
- Details of sampling plan used by the two manufacturers of the drug product.
- Difference in the drug substance concentration received by Cor (after dissolution) and the subsequent adjustment of the concentration.
- The platelet aggregation test indicated that IC₅₀ of some batches are exceeding 100%.
- Information relating to pivotal batch NO. D0015A could not be located.

3/10/97

Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

3/10/97

Eric Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:

Orig. NDA 20-718

HFD-180/Division file

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HFD-102/n [#1 only]

HFD-180/AAl-Hakim

R/D Init: EDuffy/3-6-97

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